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09/603,448	06/26/2000	Susan Margaret Thomas	M&G 10552.26-US-01	3487

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MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1637	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/603,448	Applicant(s) Thomas
	Examiner Jeffrey Fredman	Art Unit 1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 11, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-8, 11-27, 56, and 57* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8, 11-27, 56, and 57* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Sequence Rules

1. This application now complies with the Sequence Rules.

Claim Rejections - 35 USC § 112

2. The rejection of claims 4 and 6 under 35 U.S.C. 112, second paragraph, are withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102

3. The rejection of claims 1-18 and 21-27 under 35 U.S.C. 102(a) as being anticipated by Justus et al (Mutagenesis (1999) 14(4):351-356) are withdrawn in view of the declaration under 1.131.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-8, 11-14, 16-18, 21-23 and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Justus et al (Mutation Research (1998) 398:131-141) in view of Chalfie et al (Science (1994) 263:802-804)

Justus teaches a method of determining a mutagen comprising: a) contacting a test compound with a host cell comprising a DNA sequence encoding a reporter protein operably

linked to a mutagen sensitive gene such as umuC which is an SOS gene (page 133, column 1), b) monitoring a host cell preparation for reporter protein by diluting the host cells which are in logarithmic growth and incubating the host cells at 37C with shaking (page 134, column 1), where the dilution solution may starve the host cell by depleting a nutrient such as dilution into phosphate buffer (page 134, column 1), c) determining a mutagen when an amount of reporter protein meets or exceeds a predetermined threshold value (page 134, column 2). Justus further teaches detection using a range of concentrations of the test compound (page 137, figure 6). Justus teaches using analyzing a change in the shape of the data comparing a control cell with the test compound as shown on page (page 137, figure 6 and page 134, column 2).

Justus does not teach the use of green fluorescent protein as the reporter gene, nor the specific wavelengths of excitation and detection.

Chalfie teaches the use of the green fluorescent protein as a reporter gene and teaches that the protein is excited at 485 nm and detected at 509 nm (page 802, column 2).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the detection method of Justus using a luciferase reporter gene and replace the luciferase reporter gene with the GFP protein of Chalfie since Chalfie states "Several methods are available to monitor gene activity and protein distribution within cells. These include the formation of fusion proteins with coding sequences for b-galactosidase, firefly luciferase and bacterial luciferase. Because such methods require exogenously added substrates or cofactors, they are of limited use with living tissue. Because the detection of intracellular GFP

requires only irradiation by near UV or blue light, it is not limited by the availability of substrates. Thus it should provide an excellent means for monitoring gene expression and protein localization in living cells (page 803, column 3)". An ordinary practitioner would have been motivated to substitute the GFP protein of Chalfie for the luciferase reporter protein used by Justus since Chalfie notes that the GFP protein does not require exogenous cofactors, is no limited by substrate availability and can be easily detected by irradiation with UV or blue light.

6. Claims 1-8, 11-18, 21-27 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farr (U.S. Patent 5,589,337) in view of Chalfie et al (Science (1994) 263:802-804).

Farr teaches a method of determining a mutagen (column 5, ines 8-15) comprising: a) contacting a test compound with a host cell comprising a DNA sequence encoding a reporter protein operably linked to a mutagen sensitive gene (column 19, line 40 to column 20, line 19 and column 29, example 7) such as dinD which is an SOS gene (column 7, lines 3-15), b) monitoring a host cell preparation for reporter protein by diluting the host cells which are in logarithmic growth or stationary growth and incubating the host cells at 37C with shaking (column 14, lines 5-65), where the dilution solution may starve the host cell by depleting a nutrient such as dilution into minimal media (Column 14, lines 10-12), c) determining a mutagen when an amount of reporter protein meets or exceeds a predetermined threshold value (columns 29-31, example 7). Farr further teaches detection using a range of concentrations of the test compound (column 30, table 1). Farr teaches using analyzing a change in the shape of the data comparing a control cell

with the test compound as shown on (figure 9-12). Farr further teaches identification methods to detect antimutagens (column 31, example 8). Farr expressly teaches screening in 96 well microtiter plates (column 31, line 27).

Farr does not teach the use of green fluorescent protein as the reporter gene, nor the specific wavelengths of excitation and detection.

Chalfie teaches the use of the green fluorescent protein as a reporter gene and teaches that the protein is excited at 485 nm and detected at 509 nm (page 802, column 2).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the detection method of Farr using a luciferase reporter gene and replace the luciferase reporter gene with the GFP protein of Chalfie since Chalfie states "Several methods are available to monitor gene activity and protein distribution within cells. These include the formation of fusion proteins with coding sequences for b-galactosidase, firefly luciferase and bacterial luciferase. Because such methods require exogenously added substrates or cofactors, they are of limited use with living tissue. Because the detection of intracellular GFP requires only irradiation by near UV or blue light, it is not limited by the availability of substrates. Thus it should provide an excellent means for monitoring gene expression and protein localization in living cells (page 803, column 3)". An ordinary practitioner would have been motivated to substitute the GFP protein of Chalfie for the luciferase or galactosidase reporter protein used by Farr since Chalfie notes that the GFP protein does not require exogenous cofactors, is no limited by substrate availability and can be easily detected by irradiation with UV or blue light.

7. Claims 1-8, 11-27, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farr (U.S. Patent 5,589,337) in view of Chalfie et al (Science (1994) 263:802-804) and further in view of Mitchell et al (Mutation Research (1986) 159:139-146).

Farr in view of Chalfie teach the limitations of claims 1-18, 21-27 and 56 as discussed above. Farr in view of Chalfie do not teach the use of the Kolmogorov Smirnov test with selection of a P value less than .05.

Mitchell teaches the use of a Kolmogorov Smirnov test for the analysis of data regarding the ability of mutagens to effect a reporter system and show a number of Significance levels including P<.05 (page 142, table 4).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the detection method of Farr in view of Chalfie with the use of the Kolmogorov Smirnov statistical test of Mitchell since Mitchell states "It was concluded that the non-parametric Kolmogorov-Smirnov two-sample test was the most reliable method of analysis (abstract)". An ordinary practitioner would have been motivated to use the Kolmogorov-Smirnov test because it was a normal statistical analysis tool which was identified as the most reliable in determining which mutagens were statistically significant.

Response to Arguments

8. Applicant's arguments filed March 11, 2002 have been fully considered but they are not persuasive.

Applicant argues that the newly amended claim 1 distinguishes over the 35 U.S.C. 103 rejection of Justus in view of Chalfie because it incorporates the limitations of claims 10 and 24, which were not rejected. This argument is not correct because. Claim 24 originally required "growing the host cell to reach stationary phase" which distinguishes from the Justus reference which teaches using logarithmically growing cells. However, amended claim 1 states "the host cell being in logarithmic or stationary growth phase." Thus, Justus, who teaches the use of cells in logarithmic growth phase, continues to meet this element of the claim since one embodiment of claim 1 is where cells are in logarithmic growth. Applicant's argument is not consonant with the actual limitations of the claim and is therefore not persuasive.

Applicant then argues that Justus teaches away from the claimed invention by extolling particular virtues. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Justus had a preferred embodiment, this embodiment does not prevent the use of alternative embodiments or constitute a teaching away from such embodiments such as those suggested by the Chalfie reference, particularly in light of the specific motivations provided by the Chalfie reference as discussed in the rejection.

Applicant then argues that Justus does not teach analysis of a change in the shape of a data distribution. As noted in MPEP 2111,

> "During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater , 162 USPQ 541, 550 - 51 (CCPA 1969)"

In this instance, the claims broadly read include the analysis of Justus on page 137, figure 6 as a graphical representation which shows a difference in a shape of data distribution. No requirements are imposed upon this limitation so Justus's showing of a data distribution meets the requirement.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.

1992). In this case, specific motivation is provided in the rejection, which notes "Chalfie states "Several methods are available to monitor gene activity and protein distribution within cells. These include the formation of fusion proteins with coding sequences for b-galactosidase, firefly luciferase and bacterial luciferase. Because such methods require exogenously added substrates or cofactors, they are of limited use with living tissue. Because the detection of intracellular GFP requires only irradiation by near UV or blue light, it is not limited by the availability of substrates. Thus it should provide an excellent means for monitoring gene expression and protein localization in living cells (page 803, column 3)". An ordinary practitioner would have been motivated to substitute the GFP protein of Chalfie for the luciferase reporter protein used by Justus since Chalfie notes that the GFP protein does not require exogenous cofactors, is no limited by substrate availability and can be easily detected by irradiation with UV or blue light."

Applicant then argues the Farr in view of Chalfie rejection. Here again, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation is provided in the rejection, as discussed in the rejection above.

Applicant then argues that there is no reasonable expectation of success. Applicant argues that Genetech supports the position that if an embodiment were enabled in would have been disclosed. This argument is incorrect on two grounds. First, it incorrectly conflates the standards of enablement and reasonable expectation of success. For a 103 rejection, the standard is not enablement but is reasonable expectation of success.

Second, the legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e. , a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art that the Green fluorescent protein is equivalent in usage to LacZ, where Chalfie expressly indicates the equivalence stating "Several methods are available to monitor gene activity and protein distribution within cells. These include formation of fusion proteins with coding sequences for b-galactosidase (examiner notes that this is Lac Z) (page 803, column 3)". Chalfie continues on page 803, column 3 to note that GFP is superior equivalent as a means for monitoring gene activity and protein expression.. The is sufficient for a reasonable expectation of success. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that,

> In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g ., In re Geiger , 815

> F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co ., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc ., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987); In re Tomlinson ; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art directly points to the use of GFP. This is also not a situation where only general guidance was given. The prior art provides specific guidance directing the use of GFP.

Here again, the argument regarding analysis of the data distribution depends upon a narrow reading of the claims. Given their broadest reasonable interpretation, Farr teaches analysis of data distributions as shown in figures 9-12, for example, with showings of fold induction.

Finally, Applicant argues that Mitchell does not cure the defects. Mitchell expressly shows what is old in the art, that statistical analysis of biological data is well known and obvious. Further, Mitchell expressly suggests the well known K-S test.

Response to Declaration

9. The Declaration filed on March 11, 2002 under 37 CFR 1.131 is sufficient to overcome the Justus (1999) reference.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman, Ph.D. whose telephone number is (703) 308-6568.

The examiner is normally in the office between the hours of 6:30 a.m. and 4:00 p.m., and telephone calls either in the morning are most likely to find the examiner in the office.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1637

April 15, 2002